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Chapter 8: Implications of secondary findings for clinical contexts

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Abstract
Deciding how best to deal with unsought diagnostic or prognostic information provided by NGS techniques is one of the key issues for viable translation of genomics into clinical practice. The ACMG list of secondary findings is one strategy for resolving the

issue of how to deal with 'additional' genomic findings in adult care, but it is not the only model. Examples of clinical and translational genomics from the USA, UK, Australia, Germany, France, Japan, Singapore, Estonia and the Canadian province of Quebec illustrate a range of approaches to secondary or additional findings. Other cases, including testing in paediatric and prenatal populations, testing for lifestyle or wellness applications, and neonatal screening illustrate the different clinical contexts in which secondary or additional findings must be considered. In each case, practical, organisational, economic, legal and ethical aspects of dealing with secondary findings must be taken into account when deciding how best to proceed.

Key words: clinical genomics; translation; paediatric genomics, wellness genomics; health economics; secondary findings; incidental findings; return of results; international perspective

1) Introduction

Over the past 5 years several countries have initiated research projects that will set the stage for rollout of next generation genome sequencing (NGS) in the clinic. For example, the 100,000 Genomes Project in the UK (announced in 2013), the Precision Medicine Initiative in the USA (announced in 2015), and the Australian Genomics Health Alliance (AGHA) (announced in 2015) all examine the all examine the opportunities for introducing genomics into routine patient care. Implementation, whether of whole genome sequencing (WGS), whole exome sequencing (WES) or multiple panel tests, will not occur overnight; there will be a continuing need to gather data at a population level to progress our understanding of genomics, necessarily bringing clinical care into close contact with research, as research participants are recruited through the clinic, and research findings are relevant for immediate patient care. This blurring of lines between research and clinical care raises distinct ethical challenges, as the limits of our understanding of the implications of genetic variation are quickly reached. Developing clear policies to manage this potential friction is crucial to support researchers and clinicians working in this area, managing the findings from genomic sequencing and supporting individuals, as both patients and research participants, in their understanding of the implications of this data.

The results arising from genomic sequencing are often separated into two distinct categories, 1) health related findings – or findings that are 'pertinent' to the question intended to be answered by sequencing, and 2) variants that are not immediately relevant to the question, described as incidental, accidental, secondary, unsolicited, unexpected, unrelated, non-pertinent, ancillary, additional. A third category could perhaps be 3) variants of unknown significance (VUS), as, given their significance has not yet been determined, it is difficult to tell whether they might eventually be pertinent or not. VUS are usually included in category 2, however, and treated as an incidental, or secondary finding (the term used herein). The categorisation of findings is usually drawn along the lines of pertinence, rather than distinguishing between somatic or germline findings, as this is determined by the initial question.

The likelihood of secondary findings may differ in clinical care and research settings, given that genomic sequencing within the clinic is more usually initiated for diagnostic purposes, which may give rise to a more defined question being asked, and a clearer understanding of the regions within the genome that will be of interest. However, there

is still significant risk that in these explorations, other information will be unearthed that could be relevant to the patient. Understanding how to broach these occurrences in both the clinic and research are is vital, if the information has health implications. Given the clear need for guidance for healthcare practitioners and researchers working in this area, the first challenge is to define secondary findings.

The American College of Medical Genetics and Genomics (ACMG) define 'incidental or secondary findings' as: "the results of a deliberate search for pathogenic or likely pathogenic alterations in genes that are not apparently relevant to a diagnostic indication for which the sequencing test was ordered." In the UK, a report commissioned by the Medical Research Council (MRC) and Wellcome Trust (WT) (referred to herein as the 'MRC/WT report') defines them as a finding 'which is discovered in the course of conducting research, but is beyond the aims of the study'. Interestingly, the ACMG definition alludes to a deliberate search for such findings, while the WT/MRC report, in its more general description, would relate to findings both sought and those 'stumbled across' without specific prior intent.

As the previous chapters in this volume describe, secondary findings are intensely debated within the genomics community, and there is uncertainty about how best to manage them, whether they should be fed back to research participants, and if so, in what circumstance. In the clinic, opinion is divided on how best to proceed and what information the patient should receive. Secondary findings are not a challenge solely contained within genomics; in any medical specialism there might be risk of finding something about the patient's health that is not related to the initial question, for example the startling frequency with which cancer diagnoses are made in the course of Accident and Emergency department care, or tumours being detected in imaging scans that were requested for something completely different. The difference with genomics is the relative infancy of the field, the scale of uncertainty about what different findings mean, and the implications they have for a patient's health (and that of their family). The timescale of influence is also relevant – often secondary findings in other specialisms have immediate consequences for a patient, while in genomics the information could be related to a *risk* of disease where symptoms could lie decades into the future or may never materialise.

As focus on genomics continues, and more countries conduct population-level research projects to set the foundations for rollout of sequencing in clinical care, the issue of secondary findings is increasing in prominence. Researchers are universally encouraged to consider their policies on feedback of results, and are looking to their professional bodies for guidance. In response to the clear need for a position on secondary findings to support healthcare practitioners the ACMG ignited discussion on this topic with their announcement in March 2013 of a list of 57 genes deemed medically actionable. These were mutations that could lead to severe outcomes, including inherited cancers, inherited cardiac diseases, connective tissue diseases affecting the cardiovascular system, familial hypercholesterolemia, and malignant hyperthermia susceptibility. The ACMG recommended that known pathogenic (or in some cases expected pathogenic) variants discovered in any of these genes should be reported regardless of an individual's age.

The international community were largely critical of the two elements of this recommendation, one, that these variants should be actively sought, and two, that they should be fed back to the individual whether they wanted to receive them or not. For many, this undermined the ethical concept that a patient had a 'right not to know', while creating significant implications for project resource. The European Society of Human Genetics (ESHG) took a much narrower approach, advising that whole-genome sequencing be restricted to regions of the genome that were most likely relevant to the patient's potential diagnosis, with wider testing needing specific justification. Actively searching for additional findings would therefore go against this premise. In recognition that unsolicited findings would occasionally occur, the ESHG made clear that the patient's right not to know was important, although in instances where the patient is not in a position to fully understand the implications of not knowing a result, the physician may still have a moral duty to inform relatives. The general advice was to adopt a cautious approach.

In response to this criticism, the ACMG amended their recommendations in 2016 stating that 'Adherence to these recommendations is completely voluntary and does not necessarily assure a successful medical outcome.' The approach taken by the MRC/WT report was more to guide researchers in how to think about the problem, rather than prescribing a solution, acknowledging that policy would be highly project dependent, further research was needed to fully access risks and benefits to patients, and concluding that above all projects needed to think about secondary findings and draft a clear policy in advance.

Several high-profile examples from the UK demonstrate the difficulty encountered when pre-emptively designing policy. The UK Biobank recruited 500,000 participants aged between 40-69 (2006-2010) to gather health data and samples for future research. The policy upfront was that participants would not receive any results, as stated in the consent form: 'I understand that none of my results will be given to me (except for some measurements during this visit)'. When UK Biobank introduced an imaging project, this policy changed, to allow for the possibility that secondary findings might be returned, specifically relating to the findings from scans. While this is not a genomics example, it demonstrates the difficulty different projects may have in anticipating issues ahead of time, and balancing practical measures with the concerns of personnel involved in analysing results, who might feel obliged to feedback information. Part of the challenge is that patients have mixed views of how to broach secondary findings. Patients involved in focus groups that fed into the MRC/WT report offered a broad spectrum of opinion, ranging from the supportive: *"You've got the choice then to respond...and for your family to be aware also, if maybe there's a possibility it's hereditary, or there's maybe a female carrier or a male carrier with an illness."* [Focus group participant, Cardiff] to the doubtful: *"It might create unnecessary worry which potentially could lead on to psychosomatic illnesses. You think you're ill, you're going to be ill."* [Focus group participant, Cardiff].

A 2016 paper[1] questioned different stakeholders about feeding back research findings to participants that may not be related to primary project aims. This cross-sectional survey gathered views from 6944 individuals (75 countries), including members of the public (4961), genetic health professionals (533), non-genetic health professionals (843) and genomic researchers (607). The vast majority of respondents

(98%) considered treatability of the condition/disease to be paramount, but most did not expect researchers to actively search for secondary findings within a research setting. The study demonstrated that on many issues, the genetic health professionals held more conservative views than other stakeholders, which might suggest the need for further exploration of this area to better understand the disconnect between the views of the professionals, who arguably understand the implications of the data more clearly, and those of the patient.

The differences of opinion across the genomics community extend beyond just the policy approach to feeding back results. One of the major challenges within this complex discussion lies with the science itself. Clinical actionability is put forth as a useful criterion for feeding back results or not, and understandably so – if there is something that could immediately be done to improve the health of the patient, rationally, and indeed ethically, this should be promoted. Defining clinical actionability, however, is difficult. There is disagreement amongst genomics experts about which variants might be acted upon, and how, and crucially what this might mean for immediate patient care. Furthermore, clinical actionability suggests relevance to the immediate patient, however some of the results that could have major significance are related not to the health of the patient, but instead to future generations, relating to the carrier status of individuals, which may have implications for future reproductive decisions. Paediatric care similarly raises further challenges, given the timeframes for actionability – should variants relating to adult-onset conditions be disclosed to children (via their parents), and what implications might that have for their childhood and future autonomy?

This level of disagreement across different aspects of secondary findings is the reason for the need for careful consideration of policies, further discussion with patients, and better understanding of the implications of this information. The language used to describe this group of findings may influence how they are addressed by the community and received by patients. As alluded to above, ‘incidental’ is commonly used, and clearly refers to findings that were not immediately relevant to the question in hand, however the term has received criticism from patients, for the connotation of non-importance. Given these findings could refer to risk of life-threatening disease, including cancer and heart disease, they may be of huge significance to the patient, regardless of the initial clinical question. [2]

It is helpful to draw a distinction between findings that are not-pertinent to the primary clinical purpose for which NGS analysis is being carried out, but which are actively looked for, and those that are accidentally discovered, as these two groupings would require different procedures from the clinical teams involved. It would be relatively straightforward to have a policy that stipulates that findings will not be fed back, and thus states that the clinical team will not actively look for these variants. However if a variant that could have clinically significance is genuinely unexpectedly uncovered, it may then fall to the conscience of the bioinformatician about whether this should be fed back. Anecdotally, this is said to happen reasonably often, where a researcher has gone against an explicit policy because a result could have such dramatic and immediate consequence for a patient. By encouraging teams to devise policies in advance, it is hoped this scenario could be avoided, and the policy could be guided directly by the wishes of the patient.

This chapter will explore initial experiences in different nation states to understand how return of secondary and incidental findings in clinical contexts has played out so far, and what can be learnt from these approaches.

Table 1.0: Definitions provided in each case study

Country	Term	Definition
USA	Secondary findings	Actively looked for, clinically relevant
UK	Incidental findings	Secondary findings – that are actively sought after but are not related to the condition in question
Australia	Incidental / secondary	Result from analysis of the data / interrogation of genes that are not indicated by the patient's clinical presentation
Germany	Additional findings	Findings unrelated to the initial investigation/ question, but relevant for the health and/or reproductive plans of the person and/ or relatives
France	Secondary or incidental	Will not hunt for specific variants; would only return actionable results
Canada	Secondary findings Incidental findings	
Singapore	Secondary findings or incidental findings (of potential health or reproductive importance)	Incidental findings are broadly defined in the law to include what are known internationally as 'secondary findings'
Estonia	Incidental findings (or secondary)	Clinically significant unrelated to the indication of testing
Japan	Incidental/secondary findings	Non primary results; germline variants of inherited diseases that could be found during analysis of cancer tissues and blood samples using gene panels

2) International approaches to genomics in clinical care and translational medicine

Genomics is a global phenomenon, although it is not developing at the same pace or in the same way in all territories and jurisdictions. This section presents a snapshot of the way genomics is being implemented in clinical practice in a range of countries and regions. This is intended to provide a sense of how the issue of

secondary or additional findings is being dealt with in different countries with different healthcare systems and different governance regimes. Since genomics is not yet a routine part of clinical care for most patients in most states, these country profiles also review current translational genomics efforts and, where relevant, the influence of research governance on the process of the translation of genomic sequencing into the clinic.

2.1 United States

Medical practices, such as how to manage secondary findings, in the US are most often determined by the standard of care or the type of care that is expected from a minimally competent physician in the same field, with similar experience, and under similar circumstances.[3] The standard of care is often shaped by the way physicians typically manage a particular situation in the clinic. However, many states also require that clinicians do not just do what others ordinarily do, but that their actions are also those of a reasonably prudent clinician.[3] A standard of care may also be influenced by hospital policies, state or federal regulations, and statements from influential professional groups. When novel technologies, like genomic testing, enter the clinical context, the standard of care may be unclear because it takes time for a standard to develop.

When it comes to managing secondary findings in the clinical setting, there are no US state or federal regulations that directly address this issue. Thus, their management depends mainly on the standard of care that develops among clinicians handling secondary findings. In 2013, The American College of Medical Genetics and Genomics (ACMG) published recommendations regarding how to manage some aspects of secondary findings in the clinical setting. The ACMG recommended that "whenever clinical sequencing is ordered, the ordering clinician should discuss with the patient the possibility of [secondary] findings and that laboratories should seek and report [57 secondary findings]…described in [these recommendations] without reference to patient preferences."[4] These recommendations were influential in the US for various reasons, including the standing of the ACMG as a professional organization, and that they published at a time in which there was little guidance about how to manage these findings. Thus, these recommendations helped fill a gap in the standard of care. As described in more detail below, medical professionals and institutions in the US are, to a large extent, following ACMG's current recommendations regarding secondary findings.

After the ACMG published its original recommendations, there was significant backlash because many interpreted the ACMG recommendation not to ask patients whether they want secondary findings analyzed, as a violation of the tradition and legal obligation of respect for patient autonomy in the US. [5,6] The ACMG responded by modifying their recommendations to offer patients the opportunity to opt out of the analysis of secondary findings.[7] More recently, the ACMG published an updated list of the now 59 "medically actionable genes" that the organization recommends should be analysed as secondary targets, whenever clinical sequencing is performed.[8] The Secondary Findings Maintenance Group of the ACMG will periodically curate and update their list (Available at: www.acmg.net) of medically actionable genes recommended for analysis as secondary targets when clinical sequencing is performed.

Studies have examined the degree to which clinical sequencing laboratories in the US are following the ACMG guidelines. Fowler and colleagues found that 94% of consent forms examined from these clinical laboratories contained language that stipulates whether the laboratory will examine and report findings regarding the ACMG list of 59 secondary target genes.[9] Approximately 80% of clinical laboratories offered patients the opportunity to opt out or opt in of the report of some or all the 59 ACMG genes. This suggests that the ACMG guidelines have been influential in practice and that, based on their consent forms, clinical genomics laboratories in the US are following the ACMG recommendations regarding secondary findings. As the practice of offering the analysis of ACMG-recommended secondary targets in the clinical setting becomes more prevalent, a more concrete standard of practice and standard of care emerges for clinical sequencing laboratories and clinicians, respectively.

The ACMG list of medically actionable genes is likely the most influential and widely used in the US when it comes to offering secondary findings. However, it is important to note that there is no clear consensus regarding what constitutes a medically actionable gene. Geisinger Health System's My Code Community Health Initiative encourages patients to submit samples for genomic sequencing and it analyses and reports back findings from 77 medically actionable genes associated with 25 conditions.[10,11] Notably, My Code is a screening program and, therefore, strictly speaking, these would not be considered secondary findings because examining these medically actionable genes is the primary goal of this program. To further evidence the differences in what is considered a medically actionable gene that should be offered to individuals, in the research context, there are groups that have identified up to 168 medically actionable genes.[12]

The way certain issues are managed in a research context often influences how they are later managed in clinical practice. Thus, it will be important to be attentive to how projects such as the *All of Us* Research Program manage secondary findings. *All of Us* plans to recruit 1 million individuals in the US and to offer to return medically actionable findings, but the program has not determined which findings it will analyse and make available to participants, what kind of opt out alternatives, if any, or how it will return findings.[13,14] Furthermore, the US National Academies of Science, Engineering, and Medicine (NASEM) recently published a report in which it recommends that researchers carefully consider returning findings, particularly medically actionable findings, to individual research participants.[15] Thus, in the US, the trend toward offering to return medically actionable findings as secondary or primary targets is on the rise in both the research and clinical settings. On the other hand, there is much more uncertainty about what is considered a medically actionable gene, what criteria are used to determine this, and how these criteria should be applied. Since secondary findings offered in clinical care are generally medically actionable genes, it will be important to follow how this debate progresses and for groups that offer secondary findings, to be transparent about their selection criteria.

2.2 United Kingdom

The UK's major national genomic sequencing programme is the 100,000 Genomes project. The project was launched in 2013 by then Prime Minister David Cameron as a way of operationalising recommendations made in a previous UK government white paper on genetics.[16,17] Genomics England, a wholly owned company founded by the UK Department of Health, was charged with running the

project, which began recruiting through Genomic Medicine Centres located in the UK's National Health Service (NHS) in 2015. This heralded a concerted focus on genomic medicine within the NHS, seeking to exploit existing academic expertise and establish the UK at the forefront of the field, as well as to boost the country's commercial science industry. The project aimed to sequence 100,000 genomes by WGS from around 70,000 NHS patients and their families with a rare disease or adults who have cancer, as well as the less widely discussed or transparent infectious disease arm led by Public Health England.

Rare disease was chosen in an attempt to reduce the diagnostic odyssey that many patients with rare disease experience, and cancer was picked to stimulate the development of patient-specific medications by members of the Genetics Expert Network for Enterprises (GENE) consortium. This group of commercial partners have contributed financially towards the project and will have access to patient data to facilitate drug development. The project is described as 'clinical transformation' and the varied components situate it somewhere between research and routine clinical practice. Whilst this has the benefit of catalysing use of this technology in the Health Service, it also poses challenges in encouraging clinician and patient uptake.

Primary findings are fed back to patients through standard NHS pathways and were initially based on a gene-panel (via PanelApp, a crowd-sourced tool allowing curation and review of condition-specific gene panels) approach, with pathogenic variants in known disease-causing genes reported. Where this is not successful, the relevant Genomics England Clinical Interpretation Partnership (GeCIP) will be tasked with finding an answer to the clinical question. GeCIPs provide access to sequence data for over 2,500 academic and public-sector researchers and clinicians organised around particular disease categories or cross-cutting topics such as functional genomics and machine learning).

The project literature[18] makes no mention of incidental findings, however it does explain the meaning of secondary findings (referred to in the project as additional findings) defined as findings that are actively sought but not related to the condition in question. These are available on an opt-in basis and relate to a small list of serious and clinically actionable genes containing variants responsible for inherited cancer syndromes or cardiovascular disease. This list is not static however and the patient consents to receive information on all the conditions and genes on the list at the time of reporting, not those present when consenting. In children, this will be limited to information concerning childhood onset conditions. Carrier status will be reported on a small list of conditions (currently only cystic fibrosis) providing both members of a couple are recruited into the study and both consent to receiving this additional information. X-linked carrier status may be returned if appropriate. These secondary findings are returned to patients separately and at a later date compared to the primary clinical findings relating to their reason for testing.

Outside the 100,000 Genomes Project, within the NHS there are no other examples of secondary findings being routinely sought or returned. Policies concerning truly incidental findings are often *ad hoc* and vary by laboratory. In this sense the 100,000 Genomes Project policy of returning defined (if not fixed) secondary

findings could be seen to provide clarification throughout the NHS but the lack of any guidance regarding incidental findings still leaves laboratories, clinicians and patients unsure as to what constitutes best practice. As genomic medicine becomes more mainstream, a clinician's obligation to disclose genomic findings becomes complicated. There is no legislation at the current time surrounding the duties of care in genomic sequencing, and no legal duty to look for secondary findings or return incidental findings.[19] The onus therefore reverts to a duty of care or candour and what is deemed (probably retrospectively if challenged) to be the appropriate standard of care. Both the ESGH[20] and the Public Health Genomics (PHG) Foundation, a UK based health policy think-tank in genomics[21] oppose the ACMG position on secondary findings and advocate a targeted approach to sequencing.

As well as the difficulties surrounding legislation and best clinical practice, there are also concerns regarding clinical utility of secondary findings in a population context. The majority of knowledge regarding the pathogenicity of variants is derived from the traditional Clinical Genetics phenotype-to-genotype model where patients with symptoms or a family history of a condition present to the health service. Variants found in these patients can be interpreted in the context of the clinical picture of the proband or their affected family members. This is not the case in a secondary findings context. Patients will usually have no symptoms relating to the variants identified and may have no family history. Population genomic databases such as ExAC and gnomAD have demonstrated that it is possible to carry a pathogenic variant and not exhibit serious disease symptoms, leading to reclassification of certain variants. This could be due to incomplete or age-dependent penetrance, or other genetic co-factors.[22] Without further data and knowledge of the effects of secondary findings in the wider UK population, it is difficult to predict what the pathogenicity of variants are even in well-characterised disease genes.[23]

Studies have shown that the disease burden of carrying a 'pathogenic' variant in an asymptomatic person in unclear but could be significantly lower than previously suspected. [23,24] This could lead to over-diagnosis of future disease and those patients may endure unnecessary stress and worry dealing with variants they cannot comprehend, as well as additional and potential risky confirmatory tests or prophylactic treatments they may choose to undertake.[6] For this reason, a number of commentators, including a Genomic Medicine Multidisciplinary Team (GM-MDT) responsible for local review of genomic sequence data in Oxford have advocated a 'not pathogenic until proven otherwise' approach, where only variants definitively shown to be pathogenic should be fed back as secondary findings.[25] However, there is then a risk of a two-tier variant classification for primary and secondary findings which could lead to confusion for both patients and interpreting clinicians.

In summary, within the UK, the 100,000 Genomes Project is leading the way regarding clinical secondary findings in genomics and is likely to form a template for the ongoing NHS genomic medicine service. The political and medical importance of the project was reinforced in 2016 as the Chief Medical Officer chose to base her annual report on "Generation Genome". The report highlighted the potential of genomic medicine to aid the NHS in areas such as diagnostics, personalised medicine, drug discovery and disease prevention.[26] More recently, in spring 2018, the UK Parliament outlined a strategic approach to embed a genomic medicine service in

the NHS, realising the 2012 vision of transforming patient care through genetic and genomic services.[27] Seven national genomic hubs will provide genome testing for various conditions and are now planned to be operational by January 2019.[28] However, more population level data associated with clinical outcomes (including from the 100,00 genomes project itself) will be needed to help appropriately interpret genomic variants and guide counselling to patients.

2.3 Australia

In Australia, genomic sequencing tests are making a rapid transition from research to clinical practice. Australia's component states and territories are responsible for the delivery of public hospital services, which include genetic services. There is therefore a risk of divergent clinical practices arising in potentially contentious areas such as the return of secondary or incidental findings. National bodies, however, have not yet set policy which directly addresses secondary results. For the purposes of this section, the term "secondary findings'' is used to mean result from an analysis of the data/interrogation of genes that are not indicated by the patient's clinical presentation (e.g. ACMG list genes in a patient with intellectual disability).

In 2015, the Australian National Health and Medical Research Council produced a 'decision tree' for the management of findings from research and health care within their *Principles for the translation of -omics based tests from discovery to health care.*[29] Although recognising the potential for the identification and/or return of incidental and secondary findings, it simply advises following policy, patient preferences or national genomics guidelines (which do not yet exist on this issue). The Human Genetics Society of Australasia have produced a commentary on the ACMG guidelines[30], stating that they represent a significant change from previously accepted guidelines on genetic testing and advising exercising caution in adoption. The Royal College of Pathologists of Australasia recommends targeted analysis, i.e. only analysing those genes relevant to the clinical indication for testing, noting that it is a pragmatic approach to minimise the ethical dilemmas arising from "incidental" findings.[31] They also observe that, while debate and guideline development are in progress, different practices are emerging and each laboratory should provide a clear verbal and written communication of their policy.

In the Australian State of Victoria, the Melbourne Genomics Health Alliance was formed to integrate genomics into clinical practice across its member organisations.[32] These currently encompasses five hospitals, each with a genetic service, and five accredited laboratory services. Initial consultations in 2013-14 indicated that secondary findings were a concern to some medical specialists.[33] Stakeholder interviews conducted in 2015 showed that no consensus on secondary findings had emerged.[33] The Community Advisory Group, clinical and laboratory stakeholders, and ethics committees supported an approach whereby analysis and interpretation is restricted to the genes indicated by the patient's clinical presentation. Analysis and interpretation of the ACMG genes are deliberately blocked, unless a specific gene is clinically indicated.

The rationale for excluding the ACMG gene list during the early implementation of genomics in practice was as follows: Firstly, patients needed only consider the implications of their diagnostic test in pre-test counselling. Secondly, clinicians who were not expert in genetics or with little experience in genomics did not have the

additional burden of discussing secondary findings prior to testing or managing any results afterwards. In addition, laboratory workload was minimised and prioritised results of most immediate clinical use.

Publicly funded health care systems, such as Australia's, are constrained. Any increased use of resources – be they personnel time, infrastructure or consumables – have an opportunity cost. That is, those resources are not then available to provide another health service. The ratio of the cost of health intervention to the benefit it produces must be shown to warrant the allocation of resources. In Australia, national government reimbursement of new medical services and tests is largely dependent on a health technology assessment of this nature.[34] American laboratories report that the ACMG guidance has meant that they have had to incorporate a new workflow[35], but the costs and the benefits of testing have not yet been measured. Australian evidence of both the costs and benefits is also lacking.

The Melbourne Genomics Health Alliance is now assessing a sequential model for offering patients secondary findings.[36] Adults are offered a secondary findings analysis *after* the clinically indicated WE/GS results are available. This is possible since the current guidelines suggest that genomic data arising from clinical testing should be stored[31] meaning the data is available for reanalysis. The Melbourne Genomics Health Alliance refers to these as 'additional findings', in concordance with patient preferences[2] and to emphasise that it is 'extra' information arising from an additional analysis. Testing is offered with pre- and post-test counselling. If the patient accepts, their stored genomic data is reanalysed for genes predictive of actionable adult-onset conditions. These genes all have defined clinical management pathways which are publicly funded in the Victorian health system. Evaluation of this model is designed to inform health technology assessment and clinical service delivery decisions by capturing costs and assessing the process of service provision.[36] This evaluation does not provide the information needed to determine *if* secondary findings should be available but is essential to inform decisions regarding *how* they can be offered and returned.

There are at least two anticipated advantages of a sequential model for secondary findings. Firstly, if people wish to learn secondary findings, they can choose the point in their life that best suits them. This may not be when they are seeking a diagnosis or making clinical management decisions. Secondly, they have an opportunity to fully consider the implications of the secondary findings before proceeding. Genetic counsellors and patients have reported that scant attention is paid to these when diagnostic testing and secondary findings are offered concurrently.[37,38]

The concurrent model of testing – whereby consent for both diagnostic testing and secondary findings are sought at the same time – is also being tested with a cohort of infants diagnosed with congenital deafness through the Victorian Infant Hearing Screening program. Parents who consent to genomic sequencing of their infant are offered three alternatives: to restrict analysis to genes known to cause deafness; to also include analysis of genes known to cause childhood onset conditions with treatment pathways; or to include all genes known to cause childhood onset conditions. Parents' choice and experience are being captured through evaluation surveys and interviews.[39]

An international study reporting laboratory practices found that none of the participating Australasian laboratories in any state searched for secondary findings at that time.[40] There were, however, some differences in practice relating to the return of unsolicited findings; that is potentially disease-causing variants inadvertently identified in genes unrelated to the original rationale for testing. In May 2018, the Australian Government announced a AUD$500M investment over ten years in genomics research to set a robust foundation for genomic health care. With funding from the National Health and Medical Research Council, a collaboration of more than 80 organisations, Australian Genomics, is conducting a program of work to develop tools (such as a national clinical consent form) and provide evidence for the equitable, effective and sustainable delivery of genomic medicine in healthcare. Australian Genomics aims to harmonise approaches nationally by strengthening networks between clinicians, researchers and diagnostic geneticists from its participating organisations across all Australian States.[41] At the level of government, national consistency will be achieved through implementation of the National Health Genomics Policy Framework by the state and federal jurisdictions.[42]

2.4 Germany

The landscape of genomics in Germany is rather heterogeneous. Whereas panel sequencing is part of routine clinical practice, WGS and WES do not yet form part of routine clinical diagnostics and are mainly employed in basic and translational research settings. This is reflected by the status of WGS and WES within the system of reimbursement for clinical care services in German public health care. The public reimbursement system does not encompass WGS and WES as reimbursable standard health care diagnostics. NGS-panels up to 25 kb or designated as basic diagnostics are covered by the statutory health insurance system. Reimbursement of larger panels and extended diagnostics using WGS or WES is available only within special programs; in general, reimbursement has to be applied for individually through statutory health insurance.[43] Clinical use of WGS and WES is usually driven by research oriented interests and initiatives, or used within clinical contexts which are traditionally close to research such as paediatric genetics (e.g. diagnosis of rare or unknown developmental diseases). A growing number of interdisciplinary molecular tumour boards are also being established in academic oncology centres to apply NGS analyses to the diagnosis of certain cancer patients.[44]

There is no national program to promote genomic research and its implementation into the clinic comparable to the UK 100 000 Genomes Project. However, several smaller public research programs fund genomic approaches. One example is the e:Med program sponsored by German Ministry of Education and Research (BMBF), which aims to establish systems medicine in Germany. Another, the German Medical Informatics Initiative (MII), aims to establish medical data integration centres to allow for integrated analyses and research uses of clinical data from all German university hospitals, including genetic/genomic data from routine care and, ultimately, genomic data from research contexts as well.[45] One of the institutional hubs in Germany for the paradigmatic ‘‘omics’ field of cancer research is Heidelberg, with three institutions (German Cancer Research Centre, the European Molecular Biology Laboratory and the University Hospital) engaging in joint genomic activities. It is no coincidence that one of the most detailed guidelines for genomic sequencing was issued by the Heidelberg-based EURAT Group (see below).

The German Gene Diagnostic Act (Gendiagnostikgesetz, 2009) does not explicitly mention or address secondary or incidental findings. However, the parliament's official motivation for the act refers to "unexpected results" from genetic analyses ("unerwartete Untersuchungsergebnisse" 27) and to "excess (or surplus) information" ("Überschussinformationen").[46] Such unexpected results are considered to result from methods that generate information on genetic characteristics of patients beyond the medical or clinical scope of the genetic analysis. The official motivation document of the act states that during the consent process patients have to be informed about the possibility of "excess information" and "unexpected results" and should be able to decide whether they want to have 'unexpected' results returned to them or not. The act itself provides that the return of any genetic results to patients must be performed by physicians. The act thus effectively determines legal provisions within the clinical context that apply to incidental findings and which would also apply to secondary findings. It does not apply to the research context, leaving many unresolved questions concerning incidental and secondary findings in research genomics.

Several prominent German scientific organisations have published statements or recommendations concerning genetics and genomics. In 2013, the Berlin-Brandenburgische Akademie der Wissenschaften issued an "ad hoc statement on the consequences of new sequencing technologies for genetics in the clinic".[47] The statement uses the term "excess information" ("Überschussinformation") but does not discuss secondary findings or incidental findings. The same year, the German Ethics Council (DER) published a statement on "the future of genetic diagnostics".[48] As indicated by the title, the statement mainly refers to the clinical context. The DER statement does not explicitly refer to secondary or incidental findings, but refers to "excess information" and "additional result" ("Nebenbefund", literally "beside result"). The statement defines "excess information" as information, generated through genetic analyses, which is not needed for answering the clinical question of the analysis or which occurs unexpectedly or undesirably. "Additional results" are defined as results generated from "excess information" which are beyond the medical goal of a directed genetic analysis. As to practical handling, the statement mainly states that excess information and additional findings are likely to increase in the future and that pertinent ethical and legal challenges, relating for instance to the information and consent process, need to be addressed especially with respect to WGS and WES in the research context.

The German Society of Human Genetics (GfH) issued a "statement on genetic additional findings in diagnostics and research" in 2013.[49] As indicated by the title, the statement focuses on "additional findings" and chooses a differentiated approach, considering the clinical context and research context separately. The authors declare the English term "incidental finding" does not completely suit their conceptual needs and they prefer the German term "Zusatzbefund" (which might be best traduced as "additional finding"). They define "additional findings" as findings unrelated to the initial investigation or question, but which nonetheless have relevance for the health and/or reproductive plans of the person herself and/or her relatives. The term "secondary finding" is not mentioned.

In the clinical context, the authors state (in accordance with paragraph 9 of the Gene Diagnostic Acts) that consent must include information on the possible occurrence of additional findings and whether additional findings are to be communicated to the

patient. Data security, the patient´s right not to know, and the protection of people incapable of giving informed consent must also be considered. In the research context, by contrast, the report finds neither a duty to establish a diagnosis nor an obligation to report additional findings. If additional findings are likely to occur, the possibility and handling of additional findings must be clearly addressed during the consent process. If there is an agreement with the patient/participant to return additional findings, it is necessary to define a time period in which the information will be given.

Where patients and participants agree to the return of incidental findings, it is necessary to clarify which kind of results will be reported. Results have to be reliable, scientifically validated and are categorized as follows:

1. Genetic characteristics bearing a significant risk to develop a specific disease, which can be treated effectively or preventively.
2. Genetic characteristics bearing a significant risk to develop a specific disease, which cannot currently be treated.
3. Genetic characteristics bearing a slightly modified risk to develop a certain disease.
4. Genetic characteristics bearing no health related risk for the patient/participant – but which are heritable and may have consequences for reproduction.

Following the statement, information on significant health related risks that can be treated effectively or preventively (category 1) should be passed to the patient. Context-related decisions have to be made in case of other findings. The statement summarizes that communicating risks of diseases lacking treatments (category 2) as well as characteristics bearing a slightly modified risk to develop a particular disease (category 3) is of limited value. A 2016 statement by the German Research Foundation (DFG) on “human genome sequencing - challenges for a responsible application in the sciences” recognised the value of this categorization of additional findings and the attendant recommendations.

The Heidelberg-based interdisciplinary EURAT Group (Ethical and Legal Aspects of Whole Genome Sequencing) published a “Position Paper: cornerstones for an ethically and legally informed practice of whole genome sequencing”, initially in 2013 with a revised version in 2016.[50] The position paper contains a code of conduct for researchers (as distinct from treating physicians) involved in genomic research, as well as two participant consent templates. The position paper distinguishes two sorts of research findings: findings of individual health relevance for the patient that pertain directly to the sequencing request and are within the scope of actual investigation (“primary findings”), and “additional findings”, that is findings of health relevance which are non-intended and are beyond the scope of the original investigation. Echoing previous debates, the authors find the term “additional finding” more appropriate than “incidental finding” since even though it refers to unsought findings, researchers can *generally* expect to encounter findings of individual health relevance for patients when engaging in NGS analyses, so that the findings do not truly occur ‘incidentally’ even though they are non-intended.

The EURAT position paper makes the following recommendations:

1. As NGS techniques used in research may not be approved for clinical care, all findings from research (primary findings and additional findings) need to undergo clinical validation before being reported back to the patient via a physician

2. Primary findings should always be returned if they can be combined with existing knowledge and methods to provide treatment and care measures tailored to the patient's specific condition and needs, and if the patient has consented.
3. Reporting of additional findings should be part of the informed consent process. The patient has the right and burden of deciding whether or not additional findings are to be reported and if so, which findings they want to know.
4. The physician in charge must decide whether routine laboratory diagnostics will be performed in order to validate the findings and, depending on the results, communicate them to the patient.
5. The researcher has a duty of care to notify the responsible physician of all primary and additional findings that have been recognized as medically relevant for the patient, if and only if the researcher has the awareness that, in the absence of this knowledge, the patient would be subject to additional harm or increased suffering, and if the patient's statement of consent does not rule out such reporting.
6. The researcher is *not* obligated to engage in the *active* or *deliberate* search for findings beyond the specified context of a sequencing request.

The last element (6) implicitly refers to (the concept of) secondary findings as defined in this handbook (results identified based upon intentional interrogation and beyond the original scope/the patient's treated clinical condition). The EURAT statement rejects the idea of a moral or legal *duty* of researchers to actively search for findings of individual health relevance beyond the scope of investigation or disease. The EURAT Group also explicitly rejected two elements proposed by the 2013 ACMG recommendation: i) that pre-symptomatic and untreatable findings in paediatric patients be returned, and ii) that pre-specified findings be reported back to adult patients with no option to opt-out.

2.5 France

In France, genomic sequencing technologies have been used in the context of cancer and rare diseases for a number of years, but primarily in the context of clinical trials, research or clinical research projects. Only a handful of teams are using whole-exome and whole-genome sequencing tests as opposed to gene panels, which are more widespread. Indeed, neither WES or WGS are listed in the National Biology Table, which lists approved and priced acts to be reimbursed by the publicly funded, universal social security system. Until recently, there were no official French guidelines framing the return of secondary findings. Teams that had been pioneering the clinical use of these tests, therefore adapted European[51,52] or American guidelines[8] in order to establish return of results protocols that they thought would respect the best interest of patients[53]. Striking the right balance between these guidelines is challenging, knowing that the ESHG recommends that measures should be taken to limit risks of secondary or incidental findings as much as possible. Without hunting for a specific list of variants, they would then decide to return only actionable individual findings on a case-by-case basis, after collecting specific consent from patients and families, and through a consensual, collegial decision involving biologists, clinical geneticists, medical doctors familiar with the case and bioinformaticians.

However, the situation has recently changed considerably. In 2016, the Agency for Life and Health Sciences (Agence Nationale pour les sciences de la vie et la santé, Aviesan) published a report establishing a 10-year plan for the realisation of genomic

medicine in France, entitled “genomic medicine France 2025”[54]. The final recommendations stemming from the plan mandate the establishment of 12 sequencing platforms throughout the territory of France, the first two having already been identified by early 2018. The plan sets a target of sequencing over 200,000 genomes by 2025, including cancer and rare disease patients. As part of the plan, a specific WES/WGS consent form will be established, and a decision will be made on the best way to handle secondary findings at the national level.

In addition, the French Society for Personalized and Precision Medicine published recommendations on the return of actionable secondary findings in cancer genes[55]. This guideline, which specifically excludes paediatric-onset conditions, lists 36 genes in which variants are recommended to be returned to patients, including quite a few more than the ACMG recommendations. It also recommends a two-step consent, where patients are consented for the return of secondary findings not only at the pre-test counselling session, but also once the primary results are returned to them, in order to ensure they have a chance to revise their preferences at this point. It will be interesting to observe the uptake of these guidelines in practice.

2.6 Canada (Quebec)

In Canada, there are two guidelines that include recommendations on the return of secondary findings to patients or research participants. In 2015, the Canadian College of Medical Geneticists (CCMG) published a Position Statement intended to “provide recommendations for Canadian medical geneticists, clinical laboratory geneticists, genetic counsellors and other physicians regarding the use of genome-wide sequencing of germline DNA in the context of clinical genetic diagnosis”[56]. While each province and territory in Canada is responsible for determining clinical test reimbursement, this position statement aimed to provide non-binding guidance to increase consistency in clinical genomic testing offered to patients across Canada. Although the CCMG is aligned with the ESHG in stating that incidental findings should be avoided as much as possible[56], they also value individual laboratories’ autonomy and suggest ways to frame their offer to report such findings.

The fundamental document regulating research ethics is the Tri-council policy statement on the Ethical Conduct for Research Involving Humans, which stems from the Canadian Institutes of Health Research, the Natural Sciences and Engineering Research Council of Canada and the Social Sciences and Humanities Research Council of Canada. (TCPS2). This document is not legally binding in Quebec, but it is the gold standard followed by all ethics committees that oversee research in all provinces and territories in Canada. This guideline provides details on the requirements for researchers to establish a clear plan “for managing information revealed through genetic research”. Researchers are free to decide whether to share individual findings with participants, or to exclusively disclose “non-identifiable research results”. In case researchers do decide to return individual results to participants, measures should be taken so that they can:

> “(a) make informed choices about whether they wish to receive information about themselves; and
>
> (b) express preferences about whether information will be shared with biological relatives, or others with whom the participants have a family, community or group relationship.”

The “right not to know” is specifically mentioned, and researchers are required to detail how the return of results will be organized, whether directly or through a healthcare provider, as long as appropriate genetic counselling options are given to patients when necessary.

In 2014, the Quebec Ministry of Health and Social Services (MoHSS) specifically excluded the use of WES and large gene panels in patients, by adding them to the to the “list of analyses not covered by Quebec medical insurance and not reimbursed in the framework of the Authorisation and reimbursement mechanism for medical biology analyses not available in Quebec”[57]. Teams who wanted to offer those tests to patients were effectively funding them through research projects, and observed the TCPS2 guidelines regarding the return of secondary findings. However, in August 2018, the Minister of Health and Social Services Gaetan Barrette announced the creation of the Quebec Center for Clinical Genomics, located at the Ste Justine hospital in Montreal. The decision for the sequencing platform to be located in Ste Justine is mainly based on the fact that in October 2014, they initiated an Integrated Clinical Genomic Centre in Pediatrics[58] at the same site. That platform, based on the Illumina 2500 technology, started functioning in the summer of 2015, offering sequencing services to researchers in Ste Justine and other institutions in the province, and is in the process of obtaining CLIA and ISO certification to be able to offer clinically validated tests. Teams throughout the province will shortly be able to request WES or WGS tests, and a standard consent form, including guidance on how to handle secondary findings will be established, most probably using the CCMG guidelines as a starting point.

2.7 Singapore

During the rise of genomics, individual research centres and clinical units in Singapore pursued their own genomic programmes. As a result, practices concerning secondary findings varied depending on institutional capacity, expertise and ethical judgment. More recently, Singapore’s Ministry of Health has begun exploring the potential of large-scale genomics programmes for healthcare, and the National Precision Medicine Alliance has been formed as a ground-up coalition to harmonise existing genomics activities. The development of national regulations and guidelines concerning secondary findings are also providing further standardisation, depending on whether they occur in the research or clinical context.

Translational genomics research in Singapore is regulated by the 2015 Human Biomedical Research Act.[59] Amongst other provisions, the Act requires the informed consent process to disclose whether incidental findings will be returned. ‘Incidental findings’ are broadly defined in the law to include what are known internationally as ‘secondary findings’. In this section, the terms are used interchangeably. Regulations further specify that it is the responsibility of research institutions to establish institutional policies concerning the return of such findings. As of this writing, local institutions and their IRBs are in the process of developing reporting policies.

Some further guidance can be found in the Singapore Bioethics Advisory Committee’s 2015 report, “Ethics Guidance for Human Biomedical Research”, which states that there is “some duty” for researchers to report clinically significant incidental findings.[60] Non-clinically significant findings are not discussed, nor does the report go into detail concerning appropriate reporting mechanisms. It does emphasise,

however, that a reporting plan should be decided prior to commencing a study, and that the plan should be disclosed to participants – with the option of not receiving any findings, should researchers choose to make these available.

Clinical genomics is regulated separately. Beyond general professional ethics standards governing clinical practice, in June 2018 Singapore's Ministry of Health issued a Code of Practice on the standards for clinical and laboratory genetic and genomic testing services.[61] The Code defines three tiers of practice corresponding to the risk and complexity of the genetic test, with germline testing (excluding pharmacogenomic associations), occupying the highest tier. At that level, genetic counselling must be provided both before a genetic test is conducted, and at results disclosure.

The pre-test counselling must include discussion of potential incidental findings, detail the particular laboratory's policies on the matter, and explore the ramifications (clinical, social, psychological, etc.) on the return of results. In addition, the consent process must allow patients to opt in or opt out of receiving such findings. Notably, the guidelines do allow space for a laboratory to decline to report any incidental findings, as long as that policy is made clear to patients during pre-test counselling and adhered to later on. No definition of 'incidental findings' is given, nor is a standard for generating or reporting such findings (reproductive relevance, clinical relevance, clinical actionability etc.) provided. Instead, laboratories are advised to consider the clinical actionability and patient consent preferences and document the management of incidental findings in their standard operating procedures. Given that there are limited accredited genetic counsellors and clinical geneticists practising in Singapore, the clinical guidelines stipulate the pre and post genetic counselling can also be performed by a medical practitioner with several years' experience in clinical genetic counselling.

One particular risk that any pre-test counselling session should discuss is genetic discrimination. Unlike other countries, such as the US, Canada or the UK, Singapore currently lacks a legal prohibition or moratorium on genetic discrimination in insurance or employment. While there is a universal health insurance programme through MediShield Life, many Singaporeans 'top up' with private health insurance along with life or disability insurance policies. Secondary findings, then, pose theoretical but non-trivial risks to Singaporeans: when signing up for an insurance programme after having a genetic test, there is no legal prohibition on asking whether the purchaser knows they are a carrier of certain traits affecting disease risk. Likewise, similar issues could be experienced when seeking employment. Unless a moratorium on genetic discrimination is issued in future, the risk of discrimination needs to be disclosed and discussed in the genetic counselling process.

Despite the diverging regulatory regimes, there are substantial similarities in the regulations for returning incidental findings in research and clinical settings. In both cases, a plan must be in place prior to the test, disclosed to the volunteer/patient, and the option given to opt in or opt out. The type of findings returned, or whether there is a duty to generate secondary findings in the first place is at the discretion of the researcher or clinical laboratory. A substantial point of difference, though, are the pre- and post-test genetic counselling requirements present in clinical testing, but not for research. It may indeed be impracticable to require individual pre-test counselling

for large-scale genomics research, though in situations where clinically relevant findings could be generated, compromise solutions like standardised decision aids (videos, interactive apps, brochures, etc.) are worth exploring.

Clinical care and research activities are not always clearly delineated, however. For example, the SingHealth Duke-NUS Institute of Precision Medicine (PRISM) was established to transition research participants with significant genomics findings into the healthcare system for ongoing care. PRISM analyses genomic data from volunteers recruited for genomics research. Participants are then given relevant information from genetics specialists, and after counselling and consent, receive clinically validated secondary findings that are transferred to the clinical setting for follow-up care. Integrating genetic research units into clinical practice in this way requires substantial scientific, organizational and infrastructural investment, but may become more feasible as local capacity in clinical genetics and genomic research grows.

2.8 Estonia

In Estonia, research in the field of genomics and its transfer into the healthcare system has been closely intertwined with the developments of the Estonian biobank which is held by the Estonian Genome Centre, University of Tartu. The population biobank was founded in early 2000 with the long-term goal of benefiting the health of the public. Between 2002 and 2011 close to 52 000 participants were recruited, and by now all of the subjects in the biobank have been genotyped. In addition, the genomes of 2,600 and exomes of 2,500 participants have been sequenced. Although the primary goal of the biobank was research[62], the tremendous amount of genetic data that produced raises the question of incidental findings. As there are no national guidelines concerning secondary or incidental findings in population biobank settings, the practice of the Estonian biobank is based on the Estonian Human Genes Research Act which regulates its work. This legislation states that the biobank participants have the right to know results and the right to genetic counselling.[63] Currently, results are only offered on a project based manner through the biobank.[64] For example, participants detected to carry a pathogenic finding associated with hereditary breast and ovarian cancer or familial hypercholesterolemia have been re-contacted and invited to participate in a project where results are returned upon consent.[65] A second blood sample is taken to confirm the results, and validated findings are returned to the participants during a face-to-face genetic counselling session. Carriers are referred to clinical specialist for follow-up and encouraged to contact their first and second degree relatives to introduce the option of cascade screening. The response, emotions and general opinion of the participants are surveyed prior to and after the counselling session to inform future projects. As of September 2018, over a thousand individuals have received individual results and counselling at the biobank.

Clinical exome sequencing was first implemented in 2011 through a research collaboration between the Estonian Genome Centre and the children's hospitals of Tallinn and Tartu. The service was recognized as a diagnostic analysis by the Estonian Health Insurance Fund in 2014. The indication for exome sequencing covered by the health insurance fund is "an undiagnosed disease of suspected genetic aetiology, where more specific genetic analysis is not available, difficult to specify due to genetic heterogeneity or has been negative". The informed consent form for clinical exome

sequencing mentions a small possibility of clinically significant findings unrelated to the indication for testing. When consenting for exome sequencing, one can decide to opt in or opt out of being informed of incidental findings. The consent form refers to the ACMG recommendations for reporting incidental findings as well as mentioning the option of other genetic findings that could be of significant importance to the patient or relatives.[66] Based on these guidelines, the expert board of the Department of Clinical Genetics of Tartu University Hospital decide which findings are reported.

In 2015, a national personalized medicine pilot project was initiated based on the Estonian biobank.[67] The initiative foresees incorporating the genotype data of biobank participants into the national health information system to allow better targeted methods for health care and disease prevention. The approach involves targeting rare disease causing mutations (e.g. BRCA1/2, LDLR, APOB, PCSK9), polygenic risk scores for common diseases (coronary artery disease, type 2 diabetes), and pharmacogenetics. As part of the pilot phase of the initiative, clinical flagship projects have been launched involving personalized risk prediction and treatment of breast cancer and cardiovascular disease in clinical settings. In 2018, the government allocated funding for the recruitment of an additional 100 000 biobank participants.[68] Within the first five months over 52 000 individuals signed up and consented to participate in the biobank project.

2.9 Japan

In the late 1990s formal discussions about ethical issues regarding human genome research at the government level started in Japan. At that time, the Human Genome Project, of which Japan was a member, was making a rapid progress. At the same time, large genomics research programs were being promoted by the government in Japan. With this background, the Japanese government set up the Bioethics Committee in the Council for Science and Technology to lay out national frameworks to deal with ethical and social issue of genomics research.[69] In 2000, the committee issued a report on "The Fundamental Principles of Research on the Human Genome." In this document both the right to be informed and right not to be informed were stated. Based on this document, new government guidelines for genomics research, "Ethical Guidelines for Human Genome/Gene Analysis Research (*Ethical Guidelines*)" were established in 2001.[70] Although the *Ethical Guidelines* are not legally binding, they have been serving as guiding regulations across the country for more than 15 years. The Ethical Guidelines have a section describing the right of research participants to be informed of the research results, but also have stipulations on the exemptions from being informed of results. The latter includes when the disclosing the results is judged likely to harm the life, body, properties and other rights and interests of research participants. Until around 2015, many of the basic genomics research projects utilizing human samples did not adopt a policy of disclosing even primary results from genomic analysis. The main reason was because the results of the genomic analyses did not produce clinically significant data.

This situation began to change rapidly around 2015. There were several important events behind the change. First, new laws were enacted to promote and revitalize the Japanese policy for medical research in the face of an aging society. These were the Act on the Promotion of Healthcare Policy and the Act on the Independent Administrative Agency of Japan Agency for Medical Research and Development (AMED). As a result, the Headquarters for Healthcare Policy (HHP) was

established in the Cabinet in 2014.[71] One of the committees created within the HHP, the Council for Realization of Genomic Medicine (CRGM) began to steer the national policy for genomic medicine. A key report on the genomic medicine published by the CRGM in July 2015 contained a section on hurdles for implementation of genomic medicine in clinical settings. Within the section, it was stated that incidental findings were a challenging issue and requested specific government funded projects to work on it. The second important event was the establishment of a new funding agency, AMED in 2015 that coordinates funding activities for medical and translational research across the Ministries. It began to promote genomics research projects that were more relevant for clinical medicine. Even projects aiming at basic understanding of mechanisms of diseases, researchers were required to explain potential clinical outcomes of the research.

The first large project that worked on the issue of incidental/secondary findings was funded by the AMED and led by Dr. Hitoshi Nakagama, the director of the Research Institute of the National Cancer Centre. It aimed to carry out large-scale clinical sequencing in several disease areas including cancer, neuro-muscular diseases, cardiovascular diseases and others, although in the strict sense the sequencing was still research stage. The project contained a research group for ethical issues with the author of this section, Professor Kato of Osaka University, as one of its members. The group conducted literature surveys and held meetings with genomics researchers who were trying to implement clinical sequencing. It became clear that in some of the cancer areas, additional findings were being returned to sample donors, while researchers were not returning those findings in non-cancer areas. The final report published in March 2017 included five key areas of recommendations. They include the importance of providing genetic counselling, long-term follow up of patients and families, capacity building of relevant specialists such as data scientists, genetic counsellors, ethicists et cetera. Establishment of measures to prevent genetic discrimination was also mentioned.[72] Another research project is a large national genome cohort, the Tohoku Medical Megabank, which was set up after the Tohoku earthquake.[73] It was set up by the government as one of the projects for restoration of the area and has collected samples and data from about 150,000 healthy people. The Megabank also completed whole genome analysis of several thousand samples. Utilizing the results, they have started to return the genomic analysis results of familial hypercholesterolemia.

The two latest projects that are working on the issue of additional findings are also funded by the AMED. One of the projects, led by Professor Shinji Kosugi, is working on the establishment of a practical policy for returning genomic results in the clinical setting. In this project, the term “secondary finding” is used for germ line variants of inherited diseases (mostly cancer) that could be found during the analysis of cancer tissues and blood samples using gene panels. The first draft was published in March 2018 and describes necessary issues for consideration at the stages of pre-testing explanations to participants, informed consent, disclosure of results, etc. For example, the draft report recommend that at the time of informed consent, patients are given an explanation of the possibility of secondary findings and the opportunity to state their preferences of receiving the results. Another new project, known as the Leader Project (Leading the way for genomic medicine) is looking into the requirements when researchers have to deal with the secondary findings in the research setting. Also funded by AMED, the project team plans to release a final report

by March 2019. One further recent activity is worth mentioning. Japan began to perform “cancer genomic medicine,” as a part of the government initiatives to implement genomic medicine begun in 2017. Using gene panels to analyse cancer tissues, 11 designated hospitals as well as approximately 100 associated hospitals will perform cancer treatment. It is of note that none of the above activities has published a list of genes that are the targets of secondary findings.

In conclusion, a dramatic change has happened in term of the policy concerning secondary findings in genomic medicine in Japan over the last several years. A remaining challenge is to further elaborate the policy, particularly for the clinical settings. Deciding which genes (variants) need to be considered as targets of returning as secondary findings is an issue that still requires further work. It will also be necessary to work with patients to incorporate their perspectives. Effective communication and collaborations among key stakeholders including medical professionals, policy makers and patients will be the key to maximizing the benefit for the society.

2.10 Summary

The above accounts demonstrate there is no single, straightforward method for implementing genome sequencing as a routine clinical procedure. As seen in almost all the national case studies, the initial development of medical genomics has taken place in research settings and subsequently moved into clinical practice. There are important differences between the research and clinic settings. Medical research is understood as experimentation designed to produce generalizable knowledge. Medical ethicists over the years have emphasised the importance of ensuring that patients taking part in medical research do so on the clear understanding that they should not expect any therapeutic or diagnostic benefit from participation (so called therapeutic or diagnostic misconceptions). Return of findings to participants is rarely expected or even considered suitable as their clinical significance is often unknown. The regulation of medical research, through national and international laws and mechanisms such as Institutional Review Boards or Hospital Research Ethics Committees tends to focus on protection of human participants from undue harm by managing the risks to which they are exposed. Research projects also tend to have a fixed time limit and budget. In clinical care, by contrast, the injunction to ‘first do no harm’ is only a minimum basic requirement and the oversight of care is orientated towards securing the *best* possible outcome for the individual patient, which usually means securing evidence-based diagnosis and treatment. This is established in legal requirements such as the physician’s duty of care to the patient, the rules for establishing medical negligence and the concept of an established ‘standard of care’ that physicians and healthcare institutions are obligated to provide. Healthcare systems also operate in a different financial setting where costs must be met on an ongoing basis, either from a constrained budget in public healthcare settings or through the reimbursement policies of different payers (mainly insurance companies and employers) in a private system. In either case, there are well-established processes of health technology assessment (HTA) designed to assess which new processes and interventions represent value for money.

The very idea of ‘translational’ research was coined to recognise that the transition from research to clinical practice is complicated and requires work, resources, and time.[74] Translation is about more than simply developing a new

machine or procedure. It requires finding ways to make that technology work in the wider context of a particular healthcare system so that it can move from a successful prototype to a widely used, routine process.[75] Genomics presents an 'excess' of data, beyond what is needed for most diagnostic applications. Although unsought findings are not unique to WGS, the phenomenon meant that there was uncertainty about how to manage this 'disruptive' feature; for example, in the UK it remains unclear whether the established legal duty of care extends to returning additional or incidental findings in genomics to patients (and indeed potentially to their families) and if so, what should be returned. In the early stages of translation, individual clinics and hospitals must often make decisions about what should be done under conditions of uncertainty and a lack of centralised guidance. This means there is a risk of divergent standards of care emerging within jurisdictions, something widely seen as undesirable. When a new technology like WGS enters the clinical realm there is rarely economic evidence for benefit or a clear existing standard of care, and seldom time for new legislation to be passed to stipulate exactly how the technology should be used. Instead, there are more likely to be 'inherited regulations'[76] devised for earlier technologies, in this case genetic testing, and existing institutions and professional bodies that act as an authoritative reference point. In this context, the ACMG recommendations that (only) a specific subset of genomic variants should be examined for all clinical sequencing of patients can be understood as an attempt to generate a standard of care that would deal with the problem of unsolicited findings and allow the clinical implementation of genomics to proceed.

At the same time, it is clear from the studies of different territories presented above that the ACMG list of secondary findings has not been universally accepted (see table 2.0 for a summary). This should not be surprising. The ACMG approach of a defined, if flexible, list of specific genomic variants to be designated 'secondary findings' was developed in the specific setting of US healthcare. Different territories have different legal and regulatory systems, different institutions and economic underpinnings of their healthcare systems, and different cultural preferences and attitudes to topics such as risk and even defining clinical benefit. It is therefore hardly surprising that different countries and different regions within federated territories, took divergent stances on secondary findings as a solution to the problem of unsolicited genomic results. Although the ACMG list of secondary findings do not act as a universal standard of care, even in the US, they did succeed in driving forward the international debate, by prompting responses about how best to proceed, in each jurisdiction. Even though the outcomes are distinctive, there is a remarkable similarity in the mode of responses in different jurisdictions. Only Germany has a statutory provision that relates to secondary or incidental findings, and the 2009 German Gene Diagnostic Act does not actually use those terms at all, but introduces its own lexicon of 'unexpected results' arising from 'surplus information'. However, most territories deployed some form of non-binding but centralised guidelines on what best practice might look like for clinicians. These were mainly issued by existing professional bodies such as the ACMG, the ESHG, Canadian College of Medical Genetics, German Society of Human Genetics or the French Society for Personalized and Precision Medicine. Again it is not surprising that the majority of these bodies were originally concerned with the clinical provision of genetic services, as the obvious antecedent to clinical genomics. Other entities providing guidance were national bodies concerned with health research- as the originating point of medical genomics- such as the Australian National Health and Medical Research Council, AMED and the Council for

Realization of Genomic Medicine (CRGM) in Japan, the German Ethics Council and the Berlin-Brandenburgische Akademie der Wissenschaften, Singapore's Ministry of Health or the Estonian Genome Centre.

The latter example is also a reminder of the importance of projects, especially state-supported national projects, to build translational infrastructure such as biobanks to support clinical genomics.[71] Most of the examples considered above have some sort of large-scale nationally supported translational genomics venture. Some such as the 100,000 genomes project, Genomics Australia, the Aviesan plan for a network of 12 genome sequencing centres in France, the or the Quebec Centre for Clinical Genomics are new endeavours. Others build on existing infrastructure like the Estonian biobank, the Tohoku Medical Megabank, or the recent announcement that the UK government plans to extent the 100k Genomes project by sequencing a further 500,000 genomes from existing samples contained in the UK national biobank. In both cases, these translational projects provide a space where clinical implementation of genomics, including returning results, can be tested and evidence of what works or does not work generated and evaluated. They are also sites where future national policies on secondary or additional findings are likely to be formulated.

Table 2.0: Overview of stances on secondary and additional findings in national policies, guidelines and translational genomic projects

TERRITORY	LEGISLATION CONCERNING SECONDARY OR ADDITIONAL FINDINGS?	GUIDELINES ON SECONDARY FINDINGS FOR CLINICAL PRACTICE?	STANCE ON SECONDARY FINDINGS	MAJOR TRANSLATIONAL PROJECT?	STANCE ON SECONDARY FINDINGS
USA	No	ACMG guidelines	Recommend return of ACMG list of secondary findings	All of Us precision medicine cohort	Policy in development
UK	No	ESHG guidelines Public Health Genomics Foundation recommendation	Advise against return of secondary or incidental findings	100,000 Genomes project	Return project specific list of additional findings on an opt-in basis
Australia	No	NHMRC 'Principles' HGSA commentary on ACMG Guidelines Royal College of Pathologists of Australasia recommendations	Advise caution and advocate targeted use of genomics	National: Australian Genomics State specific: Melbourne Genomics Health Alliance for the state of Victoria	Pilot return of project specific list of additional findings on an opt-in basis. Australian Genomics policy is in development
Germany	German Gene Diagnostic Act (Gendiagnostikgesetz, 2009) states that potential for 'unexpected findings' must be discussed with patients.	German Ethics Council statement on "the future of genetic diagnostics"	Patients must have right to refuse additional findings. Only additional findings indicating significant risk of treatable or preventable disease should be offered for return.	Closest equivalent: BFMB e:Med program; German Medical Informatics Initiative (MII)	Not clear, but see section 2.4 for guidelines from German Society of Human Genetics (GfH), German Ethics Council and EURAT group.
France	No	French Society for Personalised and	Recommend return of expanded list of secondary findings	Aviesan network of 12 regional	Policy in development

		Precision Medicine recommendations	(more variants than on ACMG list)	sequencing platforms	
Canada (Quebec)	No	CCMG recommendations	Avoid incidental findings as much as possible but respect autonomy of individual labs and clinics to set own policy	Regional: Quebec Centre for Clinical Genomics	Policy in development
Singapore	Human Biomedical Research Act (2015) - only applies to research not to clinical practice	Ministry of Health Code of Practice	Laboratories have some scope to set own policy on returning incidental findings provided pre-test genetic counselling is provided	National Precision Medicine Alliance PRISM	National Policy in development. PRISM returns project specific list of additional findings
Estonia	No	Estonian Genome Centre policy Expert board of the Department of Clinical Genetics of Tartu University Hospital	Return of findings relating to selected cancers and familial hypercholesterolemia to biobank participants, Return of incidental findings as assessed by the expert board, for clinical genomics collaboration between the Estonian Genome Centre and children hospitals of Tallinn and Tartu	2015 National personalised medicine pilot of the Estonian national biobank	Pilot targets specific pre-defined variants associated with disease risk
Japan	No	Ethical Guidelines for Human Genome/Gene	Research participants have right to findings but also a right to opt	Tohoku Medical Megabank	Return of findings relevant to

		Analysis Research (2001) AMED-funded projects to develop policy on incidental and secondary findings	out. In practice most findings were not returned New reports in 2017 and 2018 permit return of secondary findings with appropriate consent and counselling		hypercholesterolemia only

3) Emerging and future scenarios

This section looks at a number of areas where additional or secondary findings raise new issues, or require a different perspective, in comparison to clinical genomics for adult patients with known diseases. The areas covered are; paediatric and prenatal applications of genomics; nutritional and 'wellness' genomic services; and the storage and return of sequence data to patients and research participants. Although disparate, each area represents an extension to, or, in the case of wellness genomics a spillover from, adult clinical practice. It has been noted that children challenge classifications and standards build around adults because they must be considered both a group in their own right and in terms of the future adults they will become.[77] In medicine, children are recognised to require special rules and procedures in domains from giving consent to participating in clinical trials, and returning secondary or additional findings from genomic sequencing in children also raises novel concerns about variants associated with adult versus childhood onset conditions. Wellness genomics goes beyond what is usually regarded as 'clinical' both in the sense that wellness genomic tests provide advice on lifestyle, diet, and other social activities like exercise, but also in the way that the online marketing of many wellness genomic services bypasses traditional clinical institutions and the regulations by which they are governed. Finally, return of sequence data is not a novel application of genomics, but rather an additional concern raised by the storage and digital portability of genomic data produced for the clinical applications discussed elsewhere in this chapter. Again, it is a domain where issues of secondary findings inform the broader discussion of what best practice looks like.

3.1 Pediatric, neonatal and prenatal genomics

The majority of policies on return of secondary or additional findings described above relate primarily to the clinical use of NGS techniques in adults. However, WGS WES and targeted gene panel testing are increasingly being used, or considered for use, in paediatric populations.[78] The application of genome sequencing in paediatric populations involves additional concerns beyond those discussed for adult populations in term of how to manage secondary and additional findings. At present the most frequent paediatric use of WES and WGS is in children with rare diseases.[79] These tend to be children with highly variable symptoms, such as intellectual disability, developmental delay or congenital malformation, and where there is frequently genetic heterogeneity between cases. Here, sequencing is used primarily as an aid to diagnosis. The meaning of sequence variants is interpreted in light of the patient's symptoms, as described in more detail in section 2.2.

An example of a possible secondary finding in this scenario, proposed by Klugman and Dolan,[80] would be finding a mutation in the BRCA1 gene conveying increased lifetime risk of breast and ovarian cancer, in a two-year-old child being evaluated for developmental delay using WGS. Returning this result requires consent of the child's legal guardians. Where these are the genetic parents of the affected child the result also has implications for them and for any related siblings of the affected child. One or both parents may be a carrier of the detected mutation as might an asymptomatic sibling. As with adult patients, the implications of genomic sequencing and the potential for findings to affect both patient and direct relatives need to be discussed beforehand so that adequate consent can be given.

WGS could also potentially be used to carry out population-wide screening of children for a range of conditions. The most common vision is that this would be integrated into existing public health programmes aimed at newborn children. Although not currently practiced, the idea of neonatal WGS has been suggested by several prominent sources; it was discussed as far back as a 2003 report on the use of genetic services in the UK's National Health Service[81] and has been raised by the Director of the US National Institutes of Health, Francis Collins, on more than one occasion.[82]

Screening is not diagnosis. As discussed briefly in relation to the Geisinger Health System My Code Community Health Initiative, (section 2.1), screening involves systematically testing asymptomatic individuals with the aim of detecting conditions or increased risk of disease in individuals, who can then be followed up with further confirmatory diagnosis and treatment. Current neonatal screening polices vary widely between countries in terms of which conditions are tested for and how many conditions are included in the screening procedures.[79] Moreover ACMG has explicitly stated that its list of recommended, clinically actionable variants does not apply to neonatal screening.[81] Any use of genome sequencing for neonatal screening will therefore need a policy on what to look for and which findings to return to parents. Commentaries on potential neonatal use of WGS have stressed that the clinical justification for screening is to identify conditions where preventative action or treatments can be applied during early childhood.[79,82] Screening for, or returning secondary or additional findings relating to, adult onset diseases is contrary to that rationale, although there is a further complication where a mutation indicating an adult onset condition could also have implications if one or both parents are carriers.

Another recent development has been widespread global uptake of genome-based non-invasive *prenata*l testing (gNIPT) for the detection of foetal aneuploidy, based on cell free foetal DNA fragments found and analysable in the circulating blood of a pregnant woman.[83] These fragments are reliably available for analysis from 10 weeks of pregnancy so testing can be done relatively early (although where it is necessary to send samples by post to another country this can take up to 2 weeks).[84] Cell free DNA fragments are assumed to originate from cells of the placenta, so they do pose a problem with confined placental mosaicism. Nonetheless, a recent systematic review of gNIPT for foetal chromosomal aneuploidy[85] found that genome-based testing methods appear to be sensitive and highly specific for detection of foetal trisomies 21, 28 and 13 in high risk populations and that there is a paucity of data on the accuracy of gNIPT as a first-tier aneuploidy screening test in a population of unselected pregnant women. The authors concluded that on the basis of their review, which examined 65 studies of 86,139 pregnant women, gNIPT was not sufficient to replace current invasive diagnostic tests and that invasive foetal karyotyping is still the required diagnostic approach to confirm the presence of chromosomal abnormality prior to decision making. However, Lewis et al[86] have found NIPT for the common aneuploidy Trisomy 21 to be acceptable to a vast majority of women surveyed in England. They concluded that uptake of the test is likely to be high, and includes women who currently decline screening as well as those who will use the test for information only.

The discovery of the availability of the whole foetal genome in cell free form in the circulating blood of a pregnant woman[84] also raises questions not only about the ethics of testing a foetus prenatally, but also questions about who should hold the data,

and who is responsible for 're-contacting' the future child and/or parents with genomic information, particularly should it be relevant to the health and/or healthcare of the future child. While some work has been done recently on recontacting in Europe[87] this is clearly an area where consensus about appropriate action is lacking, and where resources and desires for 'best practice' may not coincide. For both neonatal and prenatal WGS or WES, commentators have also raised the concern that returning data about genomics variants whose significance is uncertain, or where they relate to adult onset disorders could result in stress and unwarranted concern at an already stressful time for many parents and could have potentially deleterious qualities for the developing parent-child bond.[79,81]

The meaning of genomic variants depends on correlating sequence variants with phenotypic data from patient populations. This is especially challenging for neonatal and prenatal populations where limited datasets exist and most of the population are asymptomatic. Unlike the diagnostic use of WGS in children with rare diseases, there is no option for physicians to iteratively interpret the neonatal or prenatal sequence data in the context of the patient's phenotypic profile.[81] The meaning and interpretation of variants is likely to change over time as more data from more cases is added to databases[77], and this is especially the case for non-Caucasian groups who are often poorly represented in existing registries and datasets. For all these reasons, working out what, if any, data is cost effective, clinically useful, and ethically appropriate to return is especially difficult for any attempt to deploy genomics for neonatal or prenatal screening. A further issue is that establishing these genome-phenotype correlations requires making both sequence data and associated clinical information available to researchers and other clinical groups. Where existing data is limited, sharing combined datasets is likely to put the patient at greatest risk of subsequent identification, where they are least likely to receive any direct benefit from the act of sharing.[88]

3.2 Wellness genomics

Wellness is a state that encompasses physical, mental and social wellbeing, and for some, is a lifelong pursuit. Personal genomic testing, and in particular, that based upon nutritional genomics, offers new potential to those hoping to attain an optimal state of wellness. Nutritional genomics refers to the evolving study of gene-nutrient relationships, including how genetic variations influence the body's response to nutrients (nutrigenetics) and how nutrients mediate genomic function (nutrigenomics).[89] Nutritional genomics has gained increased research attention given its potential to inform an individual's optimal diet. Tailoring diet to an individual's genotype is not a new concept; diets low in phenylalanine have been prescribed to people with phenylketonuria, a genetic disorder of amino acid metabolism, since the mid-20th century. The application of nutritional genomics, however, goes beyond the clinical management of monogenic conditions, instead aiming to mitigate polygenic disease-risk in otherwise healthy populations. Initially, nutritional genomics was framed to potentially revolutionize the field of human nutrition.

Recently, the marketing rhetoric of 'wellness genomics' has emerged. In many instances, wellness genomic tests expand beyond nutritional genomics, not only offering consumers dietary advice, but insight into fitness regimens, skin care, response to medications (known as pharmacogenomics) and even personality traits. Many of these tests are available online, direct-to-consumer, although several

wellness genomic companies have moved to a direct-to-provider model.[90] In this model, a healthcare provider facilitates testing for their clients. In these instances, the healthcare provider must undergo accreditation with the chosen testing company before offering testing; however, what the training involves, and how competency is assessed, is unclear. A recent content analysis of online wellness genomic information has highlighted that in Australia, complementary/alternative medicine providers have enthusiastically adopted this testing.[91] Both the wellness genomics testing companies, and the associated complementary/alternative medicine providers, heavily market their services online. Nutritional genomics is described as the future of healthcare, suggesting that genomic wellness tests are a superior tool for facilitating health and wellbeing. Websites also claim that genomic wellness tests will reduce the guesswork around diet and lifestyle choices. In particular, websites use language such *'optimize'* and *'transform'* to describe how the test results would impact on health. Similar to other direct-to-consumer personal genomic testing advertising, the notion of consumer empowerment was paramount.[92] Unfortunately, many of the benefits of nutritional genomics have yet to materialize in most instances.

The ACCE Framework[93] provides a guideline for assessing the quality of genetic tests, especially those used to screen populations, against four criteria. Each letter represents one of the four criteria of the framework. The first, analytical validity, refers to the ability of a test to accurately identify the gene or genetic variation it intends to. The second, clinical validity, considers the reliability of a test to determine disease-risk based on a specific genetic variation. The third, clinical utility, refers to the usefulness of test results for informing healthcare decisions. The fourth criterion encompasses ethical, legal and educational domains. Testing company websites promote the tests as being evidence-based and scientifically up-to-date; some even list the clinical team involved in identifying genetic variants based on the literature.[91] However, many gene-nutrient interactions currently lack sufficient clinical validity, yet are still included in these tests.[94] Markers of poor health, such as obesity and high cholesterol, which wellness genomics attempts to combat, are mediated by the combination of genetic and non-genetic factors. Wellness genomic tests often do not take into consideration the polygenic nature of non-communicable diseases, the impact of the environment or cross-cultural differences.[95] Further, the nutritional genomics industry currently lacks regulation, meaning testing companies are free to base dietary advice on whatever evidence they choose, resulting in consumers receiving different risk-estimates depending on the company. Recognizing this, Grimaldi et al recently published a set of guidelines for assessing the validity of gene-nutrient interactions, which may produce more standardized tests in the future.[94]

Regarding clinical utility, research indicates that even when given genotype-based diets, people are unlikely to make lasting changes to their diet and lifestyle.[96] However, interviews with 16 Australian adults have revealed that wellness genomic testing is particularly enticing to the chronically unwell.[97] Disheartened by perceived negative interactions with the conventional healthcare system, the majority of these participants turned to complementary/alternative medicine in search of answers. To them, wellness genomic testing represented a new and final hope to get to the *"root cause"* of their chronic health concerns. Despite describing the test as *"empowering"* and *"validating"*, the participants' self-reported health improvements were small. Most had been prescribed new diets and a variety of supplements, but found the process was more *"trial and error"* than personalised. While these chronically unwell individuals

remained positive about their continuing pursuit of wellness, the general, healthy population looking for an 'easy-fix' to their diet may experience disappointment or 'buyer-regret'.

Given that consumers can access genomic wellness tests online or through healthcare providers who may or may not have sufficient training to interpret the results; issues also arise regarding support given pre- and post-test. Hurlimann et al [4] recommend all potential consumers be given thorough pre-test counselling to ensure informed decisions about testing are made. This is particularly pertinent when considering some genetic variants analysed in wellness genomics tests also have significant implications for non-diet related health conditions. Several wellness genomic tests use *APOE-ε4* to examine cholesterol regulation, without necessarily communicating the relationship between *APOE-ε4* homozygosity and greatly increased risk of Alzheimer's disease. [98] Recently, Janssens et al published on this issue by describing two nutritional genomic research studies in which *APOE-ε4* was included: one where the association between Alzheimer's risk was described briefly in the participant information sheet, and the other where no mention of the association was made at all.[98] The authors highlighted the potential psychosocial implications should those research participants homozygote for *APOE-ε4* later learn of their increased risk of Alzheimer's disease. However, these concerns had already become a reality for one research participant. In 2011, Messner described the case of 'Josh', an otherwise healthy 40 year old, who participated in a study investigating the impact of receiving genetic susceptibility testing on health behaviors.[99] After receiving his results, he was shocked to learn that Alzheimer's disease was one of the health conditions tested for, and that he had two copies of the *APOE-ε4* allele. Josh described feelings of hopelessness and despair, and later criticized the ambiguous consent process involved in the research.

APOE-ε4 and Alzheimer's risk is just one example of secondary or incidental findings that could emerge from genomic wellness testing. As research into gene-nutrient interactions continues, it is likely clinical validity will improve. Whether or not nutritional genomics will be the answer for those pursuing an optimal state of wellness, however, remains to be demonstrated.

3.3 Storage and return of raw sequence data in the clinical and research settings

Currently CLIA regulations (section 493.1105) require storage of analytic systems records and test reports –including genomics-based tests - for at least 2 years. For more specific suggestions pertaining to storage of NGS technology data, ACMG guidelines recommend that the genomics laboratory consider a minimum of 2-year storage of a digital file type that would allow regeneration of the primary results as well as reanalysis with improved analytic pipelines. In terms of storage of raw data, it is important to clarify what types of data resulting from WGS could be stored by the laboratories in the clinical and research settings. Data analysis based on WGS generates three file types: (i) FASTQ, which contains raw sequences with corresponding quality scores; (ii) BAM (binary alignment/map), generated by mapping of raw sequences to the human genome reference; and (iii) the VCF (variant call format) file, which contains a list of sequence variants, sorted by genomic position, at which the individual differs from the reference genome. As Evans and colleagues note, "[m]any laboratories produce an annotated VCF with numerous details (such as variant type, function, frequency in the population) to aid in the classification and

interpretation of each variant. This information, in part, is used to generate the final report for clinicians and patients."[100]

Current ACMG clinical laboratory standards for next-generation sequencing assert: "Laboratories should make explicit in their policies which file types and what length of time each type will be retained, and the data retention policy must be in accordance with local, state, and federal requirements."[101]They go on to recommend retention of the VCF and final clinical test report "for as long as possible, given the likelihood of a future request for reinterpretation of variant significance." Currently, some clinical laboratories do describe their policies relating to storage of raw data in their consent forms, informing the patients about the availability of DNA sequence data for reanalysis and storage of DNA sequence data for various purposes such as test validation or for research. In contrast, some laboratories only indicate the possibility of future policies to incorporate genetic sequence data to permanent medical records.[102] With regard to retention of files, the current practices indicate that storing VCF files and, possibly, BAM and FASTQ files by laboratories is necessary.

Long-term retention and return of raw genomic data policies may fuel a number of concerns. In terms of the retention, potential unintentional data uses resulting from long-term storage of raw data in patients' medical records (for examples by insurance companies or employers) have been underlined as a potential concern. ESHG recommendations, for instance, highlight the potential informational risks that could result from long-term storage of raw genomic data, and recommend that the potential implications of access by insurance companies and employers should be addressed.[51] Similarly, a report by PHG Foundation in the UK summarizes the main points: "It could be argued that not storing individual genomic data and re-analysing it in this way would present an enormous missed opportunity to improve both individual and population health. However, storing entire or minimal genome sequences for individual patients would require the use of electronic health records (at least in part), which has major practical and ethical implications. In addition, future technological developments may result in a substantial improvement in the quality of sequencing and genome assembly, and thus make re-sequencing an individual (as required) a better option."[103] In response, storage of raw data privately and outside the patients' medical records has been suggested as a potential solution. A recent example is MIDATA, a non-profit cooperative that offers patients private storage for a wide range of health and personal data, and allows patients to decide who should have access to the data and for which purposes.

In the context of raw data returning policies of WGS research projects, Thorougood and colleagues recently concluded that the current practices of ten projects show: "Data types and formats may differ depending on the context, sequencing platform, analysis pipelines, and evolution of common file formats. The examples of genomic data formats currently provided to participants include reduced BAM, VCF, and FASTQ."[104] Return of genomic data directly to patents and research subjects also raises the potential for individuals to use of third party websites to seek their own interpretation of the genomic data, which has been perceived by some experts as concerning. Previous studies have shown that individuals may upload their data on online platforms that provide services for interpretation of raw data, such as openSNP, Promethease, GEDMatch, and Genome Mate Pro. The features of such websites vary, ranging from returning health-related results to nonmedical traits, and genealogy.[105]

As with direct-to-consumer genetic testing services such as 23&Me, and online wellness genomics platforms, concerns have been raised about returning significant medical information to the individuals without the support and counselling provided by qualified health care professionals.[106] These questions about how much support individuals should receive from their healthcare providers in order to interpret the raw data persist.

4) **Economic dimensions of returning secondary findings from genomics in clinical routine care**

Although there are many potential opportunities from using NGS technologies, including WES and WGS, there is considerable uncertainty regarding whether they will deliver anticipated improvements in patient health. The health economic case for these technologies requires that their value to health care providers can be demonstrated.[107] This requires an assessment of their costs and benefits compared to other technologies (standard practice care), the implications for health care systems and an understanding of patient and other stakeholder views. Whilst the latter is obviously important in its own right, if fewer people undergo sequencing, this could mean that insufficient samples are sequenced in bulk, which would increase costs and reduce the likelihood that sequencing will be cost-effective. There is some evidence that applying NGS in clinical practice might improve the diagnosis and (in some cases) treatment of genetic disease. However, demand is increasing for evidence on the cost-effectiveness of these technologies compared to current practice to ensure that the technologies are not merely an expensive add-on to patient care.[108]

A recent systematic review identified only 36 papers that reported economic evaluations, cost studies or outcome studies related to WES and WGS. Most provided little detail on their study methods and generally did not consider the clinical or economic implications for patients after receiving a diagnosis.[109] Although these studies looked at sequencing in several genetic conditions, they most commonly examined neurological and neurodevelopmental disorders. Study sample sizes varied from a single child to 2,000 patients, with most studies having small sample sizes. There were large ranges in cost estimates for a single test, from $555 to $5,169 for WES and from $1,906 to $24,810 for WGS. The review concluded there was an urgent need for studies that carefully evaluate the costs, effectiveness, and cost-effectiveness of NGS technologies.

Effectively responding to secondary findings could incur significant initial financial costs, but could reduce morbidity, mortality, and overall costs, if this information helps to identify diseases at an earlier stage. Whilst there is limited health economic evidence on use of NGS generally, there is even less information on specific components of NGS, such as the use of secondary findings, especially with respect to cost-effectiveness and stakeholder preferences. A number of health economic analyses are, however, worth highlighting, including an economic decision model by Bennette et al[110] and a stakeholder survey by Regier et al[111].

Bennette and colleagues evaluated the clinical and economic impact of returning the ACMG-recommended secondary finding results.[110] They developed a decision model to estimate the likely quality-adjusted life years (QALYs) and lifetime costs associated with returning these findings in three hypothetical cohorts of 10,000 patients. These were patients with hypertrophic or dilated cardiomyopathy (two

inherited heart diseases), patients with colorectal cancer or polyposis, and 'healthy' individuals undergoing testing because family members have genomic risk factors (or family history indicates a specific disease risk). The authors concluded that returning secondary findings to patients could be cost-effective for certain populations, with QALYs increasing in all three groups. However, screening of generally healthy individuals was not cost-effective based on their calculations, unless genomic sequencing costs are less than $500 per patient. In the current climate, this is still an ambitious price for sequencing the genome of one patient. In fact, sequencing currently costs over $2,500 per patient if it is conducted within individual laboratories, as opposed to being centralised and at scale.[112]

From an economics perspective, personal utility is essentially the 'well-being' people experience from choosing a particular health care service. A Canadian study by Regier et al attempted to estimate the personal utility derived from the reporting of secondary findings.[111] They used a survey method called a discrete choice experiment to evaluate participants' personal utility for reporting secondary findings. A discrete-choice experiment is used commonly in economics (not just health economics) and market research to gather preferences from stakeholders for different attributes of a good or a service, which gives an indication of how much an individual values that good/service. By breaking down a good/service into its various attributes (characteristics), each having its own corresponding levels, survey participants are able to trade off different attributes against each other, and researchers can then see which attributes are considered the most or least important to individuals and understand whether a particular good/service is preferred.[113] Regier et al used five attributes in their discrete choice experiment investigating preferences for returning secondary findings: disease penetrance, disease treatability, disease severity, carrier status and cost, which were described in the survey in the context of hypothetical diseases.[111] The survey participants were 1200 members of the general Canadian public.

Participants indicated that they valued receiving information about high-penetrance disorders (larger proportion of individuals with the mutation who have clinical symptoms) but did not value receiving information on low-penetrance disorders (smaller proportion of individuals with the mutation who have clinical symptoms). The average willingness to pay to receive secondary findings was $445 in a scenario where clinicians returned information about high-penetrance, medically treatable disorders, but only 66% of participants indicated that they would choose to receive information in that scenario. On average, participants placed importance on having a choice about what type of findings they would receive, including receiving information about high-penetrance, treatable disorders or receipt of information about high-penetrance disorders with or without available treatment. The predicted uptake of that scenario was 76%. Although most of the people completing the survey valued receiving information on secondary findings, personal utility depended on the type of finding, and not all participants wanted to receive this information, irrespective of the potential health implications.[111] These survey findings are important because they suggest that a one size fits all approach to reporting secondary findings might not be appropriate. This evidence is interesting given the discussion earlier in the chapter about the use of wellness genomics, given that survey respondents were more likely to value the use of genomics in the context of disease management.

The limited number of health economic assessments on secondary findings have generally used health economic decision models or surveys (rather than patient level data) to examine likely costs and effects of returning information on secondary findings to patients. To fully understand the economic value of returning these findings, it will be important in the future to make use of the wealth of clinical and economic information being generated within large sequencing programmes such as the UK 100,000 Genomes Project and large centralised biobanks. These initiatives are routinely collecting resource use data, which could be used to assess the cost-effectiveness of using secondary findings in routine health care.

5) **Discussion and conclusions**

This chapter has demonstrated that when it comes to a pre-defined list of secondary findings to be routinely examined as part of genomics in clinical care, there is considerable variation between countries, and between jurisdictions within federated countries such as Australia and Canada. There are different approaches and considerations at play in different settings such as paediatric and adult clinical care, disease-focused or wellness genomics, and even in terms of which technique – WGS, WES, multiple panel testing, et cetera - should be employed. The evidence for the economic cost effectiveness of returning particular sets of secondary or additional findings is equivocal and will require further studies. Much the same can be said of the current study of patient preferences across jurisdictions, conditions, in paediatric versus adult cohorts and in terms of whether attitudes to receiving secondary or additional findings vary according to other socio-demographic characteristics.

A number of theories and models have been developed to account for successful or unsuccessful adoption of novel health technologies. These include the field of implementation science[114], normalisation process theory,[115] and the notion of an 'adoption space' where emerging technologies gain an identity as a 'cutting edge', 'life saving' or 'complicated' and 'expensive' that influences whether and where they are seen as worth adopting by hospital managers and other professional groups.[116] Although these concepts are all distinct they have some features in common. Firstly, they are rarely systematically applied to clinical genomics. Secondly, they all emphasise, in different ways, that any new technology will be operating in an existing environment of organisational frameworks, professional roles and practices, legal requirements and responsibilities, physical and technological infrastructure, social and cultural norms, expectations and values, and political and economic structures and imperatives. While a machine may 'work' according to the way it is designed, making it 'workable' –that is making it practically usable in a real world context –also requires embedding the technology in this multi-layered existing environment. This may mean adapting both the environment and some features of the technology: "technologies will always need skilled human work, inter-sectoral negotiation and a social infrastructure to ensure that they 'work'".[117]

The case of secondary findings in genomics exemplifies this translational work. As discussed above, secondary findings can be understood as a strategy to create a standard of care- an ethically and professionally acceptable way of dealing with the 'overspill' of unintended genomic results- that allows clinical implementation of NGS technologies to proceed. Secondary findings effect a separation between genomic variants whose significance is known and agreed to be serious and actionable, and those whose import is uncertain and therefore difficult to interpret or act upon. It is

intended to enable action, by providing a normative guide on how to use the technology appropriately. The fact that the ACMG guidelines have had an impact on debates far beyond the borders of the USA shows how critical resolving this tension has been in facilitating translation and making clinical genomics 'workable'. Equally, the fact that several jurisdictions are using, or trialing their own lists of secondary findings, different from those specified by the ACMG, demonstrates that while the idea is extremely useful, clear criteria for demarcating clinically actionable from not (yet) actionable variants are far from universally agreed. Genomics England, for example employs a significantly shorter list of secondary findings compared to the ACMG list while the French tradition supports looking for and returning a greater number of variants. The idea of secondary findings is therefore not a simple binary proposition – return them or do not- it is also a question of how which additional findings might be returned and how this should best be achieved.

Beyond the different criteria for clinical actionability, any attempt to implement return of secondary or additional findings also requires addressing a plethora of related 'how' issues: whether to implement 'opt-out' mechanisms recognizing patients' right 'not to know' and/or 'opt-in' mechanisms operationalizing the corollary 'right to know'; whether to provide pre-test genetic counselling and/or post-test counselling in all cases or only some; whether to return all findings in one go, or separate return of the primary result of genomic testing by leaving return of secondary or additional findings to a later date; what recontact options should be in place, especially for paediatric patients who may wish to consent to receiving additional findings on reaching the legal age of capacity; whether patients can access –or have a right to access- their 'raw' sequence data files and/or transfer them to third party analysis services; and working out whether genomic testing is being rolled out as an aid to primary diagnosis (as in paediatric rare disease), patient stratification as part of a precision medicine initiative (as in refining cancer diagnoses), or as a screening tool (as with the MyCode Community Health Initiative, and the proposals for neonatal and prenatal screening programs)?

The feasibility of each of these different options will depend a lot on the existing environment. Are enough genetic counsellors available to provide pre and post-test counselling in all cases, are recontact mechanisms in place or do they have to be created, what do existing legal instruments say about the duty of care or of confidentiality, what budget is available for different activities et cetera? Collecting and supplementing the datasets needed to make reliable correlations between genotype and phenotype also takes clinical genomics into the realms of data transfer between institutions, across borders, and in some cases between public and private sectors. This requires considerations of privacy, data protection, data ownership, and intellectual property.[118,119] That these are not simple requirements to negotiate is attested to by the ongoing work of groups like the Global Alliance for Genomics and Health (Ga4GH) which attempts to produce harmonised international standards to enable legal sharing of genomic data.[120] The heterogeneity of existing systems and their differing capacity to engage with international data flows and regulations accounts for a further chunk of the variability in the way secondary or additional findings are managed in practice .

Translation of genomics is given an additional layer of complexity because it operates in what has been termed a 'learning healthcare system'.[121] The idea of a

learning healthcare system is that new technologies can be translated by using them to provide care in the clinical context while at the same time using the data from their clinical usage to update and improve the way they are used. In the case of genomics this means integrating genomic data into clinical care while utilising genomic data collected in the clinical context to update the datasets used to correlate genomic and phenotypic data. It also means collecting evidence for the cost-effectiveness of using genomic data and returning different kinds of findings through the process of rolling these services out into clinical care. In essence this is a model of ongoing 'learning by doing'. A learning healthcare model represents a significant divergence from the clear separation of research and care that characterises traditional healthcare systems. The challenge of making clinical decisions on an evidence base that is not only subject to change but where the decision to participate actively affects that evidence base raises a number of ethical and organisational challenges, especially with regards to collecting meaningful consent from participants about what returning results is likely to mean (and that this meaning is subject to change and may necessitate future recontact).[70,122] This is particularly the case with the statistical risk associated with a particular variant in an *asymptomatic* individual, which therefore has direct relevance to secondary and additional findings.

Ultimately, most jurisdictions described here have adopted some form of exploratory implementation of clinical genomics, dealing with secondary or additional findings through smaller evaluative studies, or flagship projects that remain separate from mainstream healthcare until sufficient evidence can be collected to inform further development. In this regard, it is not necessarily problematic that different territories approach things in a different manner. Although regulatory harmonisation is often eulogised, trying different strategies in different locations affords an opportunity for organisations to learn from a wider range of experience, if- crucially- mechanisms are put in place to report on what works and what is unsuccessful in different locations and to share this information among relevant stakeholders.[123]This is a different kind of organisational learning from that envisioned by the learning healthcare system, but nonetheless may be equally relevant to clinical genomics.

A further complication is the rise of genomics services provided direct to consumer, or direct to provider (including private providers) which mix analysis relevant to clinical care with findings relating, or pertaining to relate to nutrition, wellbeing, ancestry, diet, exercise, and other lifestyle factors. As these genomic services can be presented as lifestyle, education or entertainment products, and are often marketed and sold online, they tend to escape many of the challenges of implementing clinical genomics in practice. Although desirable from a strictly economic standpoint, this is less desirable from a health protection perspective as these services may avoid having to make responsible decisions about return of secondary of additional findings and all the implementation measures that accompany them. There is seldom any provision of genetic counselling before or after testing, and policies on paediatric testing, recontact, ownership of genomic data and other aspects may be lacking or out of step with prevailing ethical and regulatory consensus. The development of coherent and responsible national and international principles for managing secondary and additional findings must therefore also consider those uses of genomics that fall outside the purview of traditional clinical services. There is a strong argument that, as ideas of agreed best practice for testing, evaluating and implementing return of primary and secondary results of genomic testing results

coalesce out of the current, exploratory translational research programmes, they should also shape the appropriate standards (e.g. provision of genetic counselling) for online and private sector genomics services whether these present themselves as health-related, educational or otherwise.

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